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Brief Clinical Report

Sibs With Cleidocranial Dysplasia Born to Normal Parents: Germ Line Mosaicism?

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Cleidocranial dysplasia (CCD) is classically an autosomal dominant disorder. However, the possibility of an autosomal recessive form of CCD has been suggested based on a report of 2 consanguineous families, one with a single affected child, the second with affected sibs, born to normal parents. We present a family with sibs with CCD born to normal parents, and suggest germ line mosaicism as the more likely mechanism for this occurrence. Am. J. Med. Genet. 69:348–351, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: cleidocranial dysplasia; germ line mosaicism

INTRODUCTION

Cleidocranial dysplasia (CCD) is an autosomal dominant generalized bone dysplasia, with complete penetrance and markedly variable expressivity [Chitayat et al., 1992]. Recently, studies have localized the gene in classical CCD to 6p21.1-21.3 [Mundlos et al., 1995; Feldman et al., 1995]. The possibility of an autosomal recessive form of CCD was suggested by a single report by Goodman et al. [1975]. He reported one family with 2 affected brothers born to unaffected first cousin parents, and a second case born from a niece/uncle union. There are several older reports of affected sibs with presumably normal parents [summarized in Lasker, 1946]. Here we present the occurrence of CCD in sibs born to non-consanguineous unaffected parents. We propose germline mosaicism as the explanation for this case, and perhaps for those previous cases of affected sibs born to normal parents.

CLINICAL REPORT

Patient 1 (Fig. 1a) presented at age 3 weeks for evaluation. Her clavicles were absent on radiograph taken after birth for suspicion of clavicular fracture. She was the 4.3 kg (>95th centile) product of an uncomplicated 42 week gestation born to a 31-year-old $G_5P_3SAB_{1(6wks)}$ woman via induced vaginal delivery.

At age 3 weeks, the infant was an active and alert child; OFC was 39 cm (90th centile), length 57.5 cm (90th centile), and she had a wide sagittal suture, large posterior fontanel, large anterior fontanel continuous with the metopic suture, and frontal bossing, with widely spaced eyes.

Radiographic skeletal survey showed additional findings consistent with CCD: tiny medial remnants of both clavicles (Fig. 1b), anteriorly rotated and relatively small scapulae with shallow glenoid fossa, and non-ossification of pubic bones (Fig. 1c). In addition, a head MRI was obtained which showed an anomalous skull base with steepness of the clivus and prominent occipital synchondrosis.

By history the parents were normal. The 32-year-old father was 181 cm tall (75th centile), and mother, aged 31 years, was 158 cm tall (25th centile). The family history was unremarkable. There were two older sibs, a 5-year-old girl, and a 2-year-old boy. Neither had CCD.

However, because of the possibility that one parent might mildly express the CCD phenotype, a detailed history, physical exam, and roentgenograms of the skull and chest of both parents were done. Results of these evaluations were normal, and it was concluded that the patient represented a new mutation.

Patient 2 presented at age 2 weeks because of findings similar to those in her older affected sister. She had been a 42-week product of an uncomplicated pregnancy, 3.7 kg (75th centile), 55.5 cm (90th centile), born by normal vaginal delivery. Amniocentesis was done due to maternal age (33 years), and chromosomes were normal.

The infant had a brachycephalic skull, wide sagittal suture, large anterior and posterior fontanels, hypertelorism (interpupillary distance 4.6 cm, >97th centile), Wormian bones, hypoplastic remnants of both

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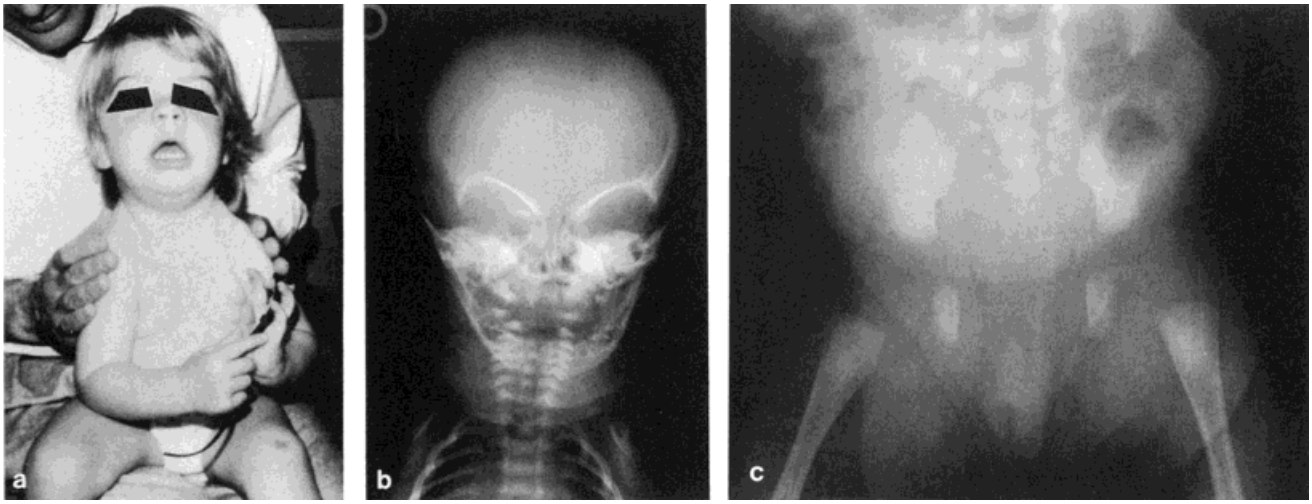

Fig. 1. **a:** Patient 1 at age 2-1/2 years. **b:** AP skull and chest radiograph. Note the severely hypoplastic clavicles. **c:** Radiograph showing absent ossification of the pelvic bones.

clavicles (Fig. 2), and no ossification of pelvis or distal phalanges, and thus the diagnosis of CCD was made in her as well.

DISCUSSION

Cleidocranial dysplasia is considered an autosomal dominant disorder, with complete penetrance and markedly variable expressivity, with 20–40% of cases representing new mutations [Martinez-Frias et al., 1988]. Affected individuals usually are short [Jenson, 1990], have a large and late-closing anterior fontanel, absent or hypoplastic clavicles, and various dental anomalies. However, in some families, affected individuals have only mild clinical manifestations. In a family reported by Chitayat et al. [1992], 2 affected individuals had only clavicular hypoplasia. Both of our patients had classic CCD and the parents had no signs consistent with this diagnosis, either on clinical or radiographic evaluation. This would indicate that CCD in this family is either an autosomal recessive trait or an autosomal dominant with germ line mosaicism. Nonpaternity is another possibility. This is unlikely because of a concurrent recessive disorder, sucrose isomaltase deficiency, in one affected and one unaffected sib.

Germ line mosaicism has been proved in the unaffected father of affected sibs with perinatally lethal osteogenesis imperfecta [Cohn et al., 1990; Byers et al., 1988], von Willebrand disease [Murray et al., 1992], EDS type IV [McGookey-Milewicz et al., 1993], and neurofibromatosis type 1 [Lázaro et al., 1994]. Long-term follow-up in other cases has shown that individuals with a presumed autosomal recessive disorder had affected children. This has been seen in Larsen syndrome [Petrella et al., 1993], and pseudoachondroplasia [Hall et al., 1987; Hall, 1988].

In addition to the previously cited instances, germ line mosaicism has been noted to occur in other autosomal dominant skeletal dysplasias, notably achondroplasia [Fryns et al., 1983; Reiger, 1984], Crouzon syndrome [Rollnick, 1988; Navarette et al., 1991], Apert syndrome [Allanson, 1986], and spondyloepiphyseal dysplasia [Mulla et al., 1994]. In addition, germ line mosaicism would explain the occurrence of affected sibs in campomelic syndrome, recently localized to 17q24.3-25.1 [Tommerup et al., 1994].

The evidence for an autosomal recessive form of CCD is scant. Goodman et al. [1975], reported on 2 affected brothers born to unaffected (by physical and x-ray

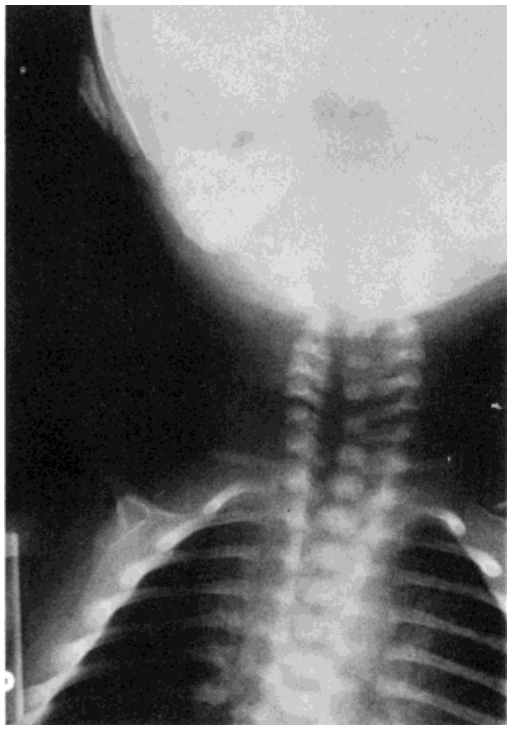

Fig. 2. Chest radiograph showing severely hypoplastic clavicles.

TABLE I. Previous Reports of Sibs With CCD and Normal Parents [Lasker, 1946]

Number of affected sibs	Family	Report
2	Affected same-sex twins	Hesse, 1925
	Affected brother and sister	Preleitner, 1903
	Affected brothers	Steindler, 1929
	Affected sisters	Lopez Pondal, 1941
	Affected brothers	Lyons and Sawyer, 1944
3	2 affected brothers, 1 affected sister	Ruggeri, 1940
4	4 affected brothers	Johns, 1915

exam) first cousin parents of Jewish Iraqi origin, suggesting autosomal recessive inheritance. The second case was the product of a niece/uncle marriage also of Jewish Iraqi origin, whose father was 31 years old at the birth of this child, possibly demonstrating a new dominant mutation due to parental age effect [Risch et al., 1987]. The consanguinity in these cases may be misleading, however, as the overall consanguinity rate of the Iraqi Jewish population is 28%, while that of first cousin marriages is 17%. Thus, this first family could be an example of germ line mosaicism.

Lasker [1946] presented pedigrees of 73 families with more than one affected individual, and he stated that in a few instances there were affected sibs born to phenotypically normal parents. These include one set of same-sex twins [Hesse, 1925], 4 sibships with 2 affected sibs [Lopez Pondal, 1941; Lyons and Sawyer, 1944; Preleitner, 1903; Steindler, 1929], one sibship with 3 affected sibs [Ruggeri, 1940], and one sibship with 4 affected siblings [Johns, 1915] (Table I). These may also represent germ line mosaicism. However, complete examinations of the parents were not done, and one cannot totally eliminate the possibility that one parent might be mildly expressing the CCD phenotype.

In conclusion, our case, the case of Goodman et al. [1976], and several prior reports may be examples of germ line mosaicism. This can be confirmed only after the CCD gene has been identified and molecular mutations have been characterized. Caution should be exercised when counseling a family after the birth of an apparently isolated affected child with CCD.

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